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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/693,120	10/20/2000	Dosuk D. Lee	04712/027002	7808

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EXAMINER	
SHARAREH, SHAHNAM J	

ART UNIT	PAPER NUMBER
1617	7

DATE MAILED: 08/27/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/693,120	LEE ET AL.	
	Examiner	Art Unit	
	Shahnam Sharareh	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *6/602, 10/20/2000* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *22-44* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *22-44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Pri rity under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicant's election without traverse of group II claims 22-44 in Paper No. 6 is acknowledged. Claims 22-44 are pending.

Priority

An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification or in an application data sheet (37 CFR 1.78(a)(2) and (a)(5)).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 24 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for adjuvant compositions comprising calcium phosphate and an anticancer agent, does not reasonably provide enablement for compositions containing any anticancer derivative and calcium phosphate. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

The recitation of "derivatives thereof" in claim 24 directs the claim to encompass a plethora of compounds, the scope of which is not enabled. Specifically, determining the toxicity and efficacy of all such compounds for *in vivo* use require undue experimentation. The specification does not provide guidance as to how one skilled in

the art would go about selecting a derivative of choice in forming the instant compositions. Nor is guidance provided as to a specific protocol to be utilized in order to prove the efficacy of the presently claimed compositions in eliciting the desired response. Further, there are neither working examples nor teachings in the specification that enable one skilled in the art how to first identify the desired derivative, and second determine the desired ratio strength, doses or even safety of the incorporated derivative in order to practice the claimed invention. Therefore, the amount of guidance presented in the specification fails to present a required amount of guidance to perform the claimed invention without undue experimentation.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 22-44 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "poorly" in claim 22, 27, 30, 33 is a relative term which renders the claim indefinite. The term "poorly" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

The recitation of “derivatives thereof” in claim 24 renders the claim indefinite. The recitation of “derivatives thereof” encompass various possible moieties, the metes and bounds of which are not clear. Each individual compound of claim 24 can contain

numerous functional or non-functional derivatives, however, specification fails to define the scope of such derivatives. Thus, the claim as a whole is indefinite.

In claim 40, the use of the limitation "anticancer therapy" is ambiguous. While applicant may be his or her own lexicographer, a term in a claim may not be given a meaning repugnant to the usual meaning of that term. See *In re Hill*, 161 F.2d 367, 73 USPQ 482 (CCPA 1947). The term "anticancer therapy" in claim 40 is used by the claim as a means to " decrease the tumor mass," while the accepted meaning is a therapy that "decreases the tumor mass."

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 22-23, 25-30, 32-41 are rejected under 35 U.S.C. 102(b) as being anticipated by Gerhart et al US Patent 5,085,861.

Gerhard disclose calcium phosphate containing compositions comprising biocompatible calcium phosphate ceramics that can be in the form of an injectable or moldable paste and will solidify within 10 minutes after administration. (see abstract; col 7, lines 30-46, 60-67; col 8, lines 1-20; examples 2-3). The particle size of Gerhard's compositions falls within the instantly claimed nanocrystalline (see col 7, lines 15-25). Gerhard's compositions contain active agents that are readily used in treatment of cancers such as bone tumor (col 13, lines 45-67). Gerhard finally discloses kits for

preparing his composition for ease of use in a clinical or surgical setting (col 7, lines 42-49). Accordingly, Gerhard anticipates the limitations of the instant claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

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Claims 22-44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kossovsky et al US Patent 5,462,751 in view of Constantz et al US Patent 5,782,971 and further Relyveld US Patent 4, 016,252 and Gupta et al (Vaccine Design, Chapter 8 pp 229-248, 1995).

The instant claims are directed to paste compositions comprising calcium phosphate and an anticancer and kits thereof containing a second adjuvant and means to deliver the composition.

Kossovsky et al teach compositions comprising calcium phosphate (brushite) compositions that are suitable for delivery in immune response eliciting moieties such as peptides and proteins (abstract, example 1-2). Kossovosky's composition can further contain an anticancer agent such as taxol (see example 16). The brushite particles of Kossovsky are less than 1000 nm, more specifically 5 nm to 150nm (col 3, lines 62-65; col 6, lines 52-55). Kossovsky states that because of its small particles their nanoparticles can avoid being removed from circulation by RES, thus providing motivation to the size properties of his drug delivery systems. Kossovsky also teaches coating of his core complex by using a second type component such as Cellobiose (a natural polymer) to enhance specificity of his formulations (abstract, example 2). Kossovsky, however, fails to specifically teach a hardenable paste formulation for injection.

Constantz et al teach amorphous calcium phosphate containing compositions that are used as suitable drug delivery vehicles (col 2, lines 60-67; col 6, lines 61-63). Constantz specifically teaches paste formulations of calcium phosphate that are

capable of hardening after administration at the site of interest (col 6, lines 40-64). Constantz's composition comprise about 15 wt% of the dry ingredient (solid component) having particle sizes of about 0.5- 500 microns (col 5 lines 1-3; and lines 14-25). Constantz further indicates that one of ordinary skill in the art would be able to modify the viscosity of his composition by varying the percentages of solids in his composition, thus allowing for ease of administration (col 6, lines 32-39). Constantz suggests the use of an additional calcium phosphate and also states that the calcium to phosphate ratio of such compositions should be about 1.6 to about 1.8 (see col 3, lines 5-20; col 5, lines 1-10, claims 1-5). Constantz finally suggests preparing kits to ease access and preparation (see col 7, lines 1-10). Constantz lacks the specific teaching of an anticancer agent in combination with the calcium phosphate vehicle.

Relyveld and Gupta are used to show conventional nature of of the calcim phosphate paste systems. Specifically, Relyveld teaches methods of delivery of a bioactive agent using calcium phosphate gels (an amorphous formulation) as an adjuvant wherein the calcium to phosphate ratio is from 1.62 to 1.85 (col 2 lines 1-15). Gupta teaches calcium phosphate compositions that can be used as adjuvant in vaccine (see page 239, 241 sec 3.2). Gupta specifically teaches that the quality of calcium phosphate products depends on the concentration of reactants, and the rate at which the reactants are mixed (page 240). Finally, Gupta teaches that the potency of vaccine formulations can be increased by incorporation of other adjuvant-active components (page 241, last paragraph).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time of invention to modify concentrations and calcium phosphate ratios of Kossovsky to suitable parameters, as suggested by Constantz, Relyveld and Gupta, by modifying the percentages of the calcium phosphate component of Kossovsky and formulate a hardenable calcium phosphate formulation that is easily administered to a site of interest such as a tumor.

Furthermore, one of ordinary skill in the art would have been motivated to incorporate a second adjuvant, separately, as taught by Gupta; or in the form of a coating, as taught by Kossovsky's patent, to enhance the therapeutic efficacy of calcium phosphate containing therapeutic composition. Finally, the ordinary artisan would have had a reasonable expectation of success in preparing a ready to use kit for easing the access and use of such compositions at a clinical setting.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 22-44 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 22-44 of copending Application No. 09/692,664. Although the conflicting claims are not identical, they are not patentably distinct from each other because both claimed inventions are directed towards compositions comprising calcium phosphate and an anticancer agent. The only difference between the two applications is that the instant claims use nanocrystalline or poorly crystalline calcium phosphate. Nevertheless, it would have been obvious to one of ordinary skill in the art at the time of invention to practice the instant invention using any species of calcium phosphate including the instant nanocrystalline or poorly crystalline calcium phosphate, because the ordinary artisan would expect the same clinical outcome.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

No claims are allowed. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shahnam Sharareh, PharmD whose telephone number is 703-306-5400. The examiner can normally be reached on 8:30 am - 6:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Minna Moezie, JD can be reached on 703-308-4612. The fax phone numbers for the organization where this application or proceeding is assigned are 703-

308-4556 for regular communications and 703-308-4556 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1123.

RUSSELL TRAVERS
PRIMARY EXAMINER
GROUP 1200

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August 21, 2002